Dear Editors and Reviewers,

Thanks for taking the review so carefully, and with your help we have the opportunity to improve this article. We appreciate the valuable comments you have made, each of which we strongly agree with, and we have followed the suggestions to make revisions. We are sure it will all be a meaningful work.

Major points

1. The manuscript should be reviewed for spelling mistakes.

Response 1

We agree with your comments and thank you for your careful examination. In this revision, the article has been completed with further linguistic touches, we have refined and revised the entire text, and the language certificate has been provided in the attachment.

2. It is said that there is an English certificate, but a form that does not belong to an institution has been uploaded. Details should be shared about whether there is a person at a level that can issue a certificate about the person who signed this letter or this certificate should be obtained from an institution.

Response 2

Sincere thanks for your suggestion. To improve the quality of the article, we have invited a professional native English speaker to proofread the article and we believe we can meet your requirements. The language certificate can be found in the attachment.

3. The reference units in the laboratory values section are not written in the article, they should be added.

Response 3

Thank you for your careful review. We proofread the whole draft again, and made corresponding changes to the section on laboratory tests, and improved the units of test values for more standardized and accurate expression. The relevant revisions can be found in line 136-153:

Laboratory examinations: Blood tests indicated WBC of 6.51×10^9/L (reference range: 3.5–9.5×10^9/L), LYMPH of 0.9×10^9/L (reference range: 1.1–3.2×10^9/L), neutrophil percentage (NEUT%) of 78.5% (reference range: 40–75%), triglycerides (TG) of 3.16 mmol/L (reference range: <1.7 mmol/L), creatine kinase of 19 IU/L (reference range: 26–200 IU/L), lactate (LAA) of 3.92 mmol/L (reference range: 0.5–2.96 mmol/L), hs CRP of 5.02 mg/L (reference range: <3.0), ANA antinuclear antibody of 1:320 nuclear granule type, CRP of 0.645 mg/dL (reference range: <0.8 mg/L), ESR of 5 mm/h (reference range: 0–20 mm/h), IgG of 663 mg/dL (reference range: 694–1620 mg/dL), serum IgG2 of 92.8 mg/dL (reference range: 169–786 mg/dL), CD3+ T-cell count of 684.2 cells/μL (reference range: 835–2217 cells/μL), CD3+CD4+ T-cell count of 267 cells/μL (reference range: 395–1264 cells/μL), NK cell count of 46 cells/μL (reference range: 136–880 cells/μL), CD19+ B-cell count of 65.58 cells/μL (reference range: 92–498 cells/μL), glycosylated hemoglobin of 7.1% (reference range: 4–6%), normal RF, and no significant abnormalities seen in coagulation function. Cytokine-related assays, such as interleukin (IL)-2, IL-3, and IL-6, were not significantly abnormal, and angiotensin-converting enzyme was not abnormal.

4. The names of the hospitals to which the patient applied were given before, but I think that the hospital name should not be given ethically, as it will be perceived as disparaging these hospitals. The other hospital names should be removed from the article

Response 4

We quite thank you for the comment. We strongly agree with you and have made changes in the corresponding part of the article. As you said, the existence of the name of the hospital may be ethically questionable, so we only kept the name of the hospital where the patient visited this time, hoping to present the case in a more standardized way. The relevant revisions can be found in line 99-122:

History of present illness: Sixteen months ago, the patient developed edema of both lower limbs (calves) without any obvious cause, which was aggravated by prolonged standing and slightly relieved by lying down. Subsequently, the redness and swelling increased, spreading from calves to knees and feet with skin stiffness. The patient was diagnosed with "lymphangitis of both lower extremities" in a local hospital, and was given anti-inflammatory and magnesium sulfate topical treatment, but the treatment did not have an obvious effect. The patient then gradually developed redness and swelling of both upper extremities, which later worsened with skin stiffness. Ten months ago, she consulted the local hospital for redness and swelling of the extremities and skin stiffness without significant improvement, and was considered to have "scleroderma", and skin pathology biopsy resulted in a diagnosis of "suspected eosinophilic cellulitis". Six months ago, the patient was seen again at the above hospital, where she was diagnosed with EF after a supplemental antinuclear antibody profile test showed ANA 1:1280 speckled. Prednisone acetate 60 mg once a day orally was prescribed for anti-inflammation, and intravenous cyclophosphamide 200 mg was given to control her condition; symptoms then improved. After discharge from the hospital, the prednisone acetate dose was reduced by 5 mg every three weeks, and oral cyclophosphamide 4 tablets once a week were started after one month. Two months ago, due to the aggravation of the condition, the patient was given prednisone acetate 40 mg, cyclophosphamide intravenously to control the disease, and leflunomide 10 mg once a day, and her symptoms were relieved more than before.

5. It is said that the patient was given hormone therapy, but which hormone was not mentioned. Details about hormone therapy should be given.

Response 5

Thank you for your careful review. We have added the type of hormone in this version of the manuscript. The hormone used since the onset of the patient is the same specification of prednisone acetate. The relevant revisions can be found in line 114-122, 161-173:

Prednisone acetate 60 mg once a day orally was prescribed for anti-inflammation, and intravenous cyclophosphamide 200 mg was given to control her condition; symptoms then improved. After discharge from the hospital, the prednisone acetate dose was reduced by 5 mg every three weeks, and oral cyclophosphamide 4 tablets once a week were started after one month. Two months ago, due to the aggravation of the

condition, the patient was given prednisone acetate 40 mg, cyclophosphamide intravenously to control the disease, and leflunomide 10 mg once a day, and her symptoms were relieved more than before.

Combined with the symptoms and signs and ancillary tests, the diagnosis was considered EF with suspected scleroderma. The selected treatment regimen included oral prednisone acetate 25 mg once daily, leflunomide 10 mg once daily, and immediate intravenous cyclophosphamide 0.4 g. The patient was a young woman and we intended to adjust the treatment regimen to methotrexate 10 mg once a week and mycophenolate mofetil 0.5 g three times a day to ensure reproductive function; however, the patient refused this option due to financial factors. Therefore, the final regimen was prednisone acetate 25 mg once daily (reduce the dosage by 5mg every three weeks) cyclophosphamide 100 mg orally every other day and leflunomide 10 mg orally once a day. The patient was asked to calculate the cumulative amount of cyclophosphamide and adjust the regimen when it reached 12.0 g or when menstrual disorders appeared.

6. In the literature, drug-induced EF is mentioned. Is there a factor that they think may be involved in the etiology of this patient? for example, the drugs he used for diabetes. this description can be added to the manuscript.

Response 6

We admire the academic rigor of the reviewers and we have learned a lot from this revision that has greatly improved our standard. Couldn't agree more with each of your comments, which will greatly improve the quality of the manuscript. Regarding the presence of drug triggers, we have detailed in the article that the patient denies any history of other previous medication use, and all traces of the revisions can be found in the manuscript. We consider that the patient's DM was caused by the slow application and reduction of prednisone acetate, and that the patient's medications applied in this visit, such as hypoglycemic drugs, were started after the onset of EF. We also added to the previous literature on EF triggers that there was not sufficient evidence regarding the patient's current application of medications to support the possibility of triggering or exacerbating EF, so we will not consider the possibility of drug-induced EF more for now. This is added to the section “Discussion” and the relevant revisions can be found in line 206-220:

The onset of the disease may be induced by a history of strenuous exercise or by exposure to certain drugs (such as statins, ramipril, heparin, pembrolizumab, immune checkpoint inhibitors, and anti-tumor necrosis factor drugs)[7, 8], while in many patients no clear cause has been found, as in the present case. The patient denied a history of muscle strain and trauma prior to the onset of the disease, as well as the application of medications that could have contributed disease onset. During the treatment of this patient, in addition to the conventional drugs for EF (prednisone acetate, cyclophosphamide, and leflunomide), hypoglycemic drugs such as metformin and human insulin, and calcium carbonate tablets, osteoporosis triol gel, and compound sulfamethoxazole were used to treat EF complications, i.e., diabetes, osteoporosis, and prevention of infection. However, there is no previous evidence that these drugs may have contributed to the development and exacerbation of EF. The patient had no

suspicious medication history prior to onset, so the possibility that the drugs caused EF was ruled out.